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Kidney and anemia in familial amyloidosis type I

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Background. Familial amyloid polyneuropathy (FAP) type I is caused by a mutated transthyretin (TTR V30M) and characterized by a sensorimotor and autonomic neuropathy. Renal, cardiac, and ocular abnormalities can also occur. Anemia has been described in previous reports, but its prevalence in Portuguese FAP patients is not precisely known. The aim of this study was to estimate the prevalence of anemia in FAP type I Portuguese patients and to evaluate the contribution of erythropoietin (Epo) to its genesis.

Methods. A retrospective cross-sectional study was undertaken to determinate the prevalence and characteristics of anemia in 165 FAP patients. For comparison analysis, 3 control groups were also evaluated, 1 group of 46 apparently healthy subjects, 1 group of 17 asymptomatic carriers of FAP-trait, and a group of 14 non-FAP patients with chronic renal insufficiency. Serum Epo levels were analyzed in all groups.

Results. Anemia was present in 24.8% of symptomatic FAP patients. Iron stores, B12 vitamin, and serum folate levels were normal. FAP patients presented significantly lower serum Epo levels than healthy controls ($P = 0.003$). Epo levels were found lower than expected for the degree of anemia and in 17.5% were undetectable. Low Epo values were observed independently of the presence of renal failure or anemia, and sometimes preceded clinical disease.

Conclusion. Anemia in FAP type I is a common manifestation. The results clearly suggest a defective endogenous Epo production in the genesis of the anemia.

Familial amyloid polyneuropathy (FAP) type I (Portuguese-type) is the most common form of hereditary amyloidosis, caused by an amyloidogenic variant of thransthyretin with a substitution of methionine for valine at position 30 (TTR V30M). This hereditary disease, of autosomal-dominant transmission, has a high prevalence in Portugal. In fact, Portugal represents the largest focus of disease worldwide, and the carrier frequency in the region of Povoa de Varzim/Vila do Conde was estimated at 186×10^{-5}, 1 in every 538 individuals [abstract; Sousa A, *J Rheumatology* 20:190, 1993]. The main expression of this disease is a sensorimotor and autonomic neuropathy, but other manifestations, such as nephropathy (proteinuria and renal failure), ocular, and hematologic abnormalities can occur. The disease is progressive, highly disabling, and death occurs on average 11 years after the onset.

Anemia in FAP V30M is not well characterized. Moderate normocytic normochromic anemia was observed in 39% of the Swedish FAP patients and classified as anemia of chronic disease with iron metabolism abnormalities [1]. Macrocytic and hypochromic anemia was reported in a group of 35 Japanese FAP patients [2]. In a previous study of 38 Portuguese anemic FAP patients, we have shown that serum levels of erythropoietin (Epo) were low for the degree of anemia [3]. Normalization of iron status was insufficient for the correction of anemia, which responded, however, to the administration of recombinant human erythropoietin [3].

In order to evaluate the dimension of this problem in a large Portuguese FAP population, a retrospective cross-sectional study was undertaken to determine the prevalence and characteristics of anemia in a representative sample of the FAP population, and to define the demographic, clinical, and laboratory data associated with anemia.

METHODS

FAP patients

Clinical data from 165 patients, randomly selected from a total of 400 FAP patients followed at our outpatient clinic, were collected for the present analysis. All patients had the TTR V30M mutation confirmed by the detection of TTR Met30 in serum, using immunoblotting procedure, and by DNA analysis. FAP patients submitted to liver transplant, with concomitant pathology, or being treated with myelotoxic drugs, were excluded. The sample population consisted of 90 males aged 21 to 71 years,

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and 75 females aged 28 to 73 years. The disease had, on average, an evolution time of 6 years (0.5–18 years). The age at onset of symptomatic disease was, on average, 35 ± 11 years, as expected in the Portuguese FAP population [4].

Control groups

A group of 46 apparently healthy adults (15 males, 31 females, aged 26 to 68 years), randomly recruited among the population of blood donors of Santo António General Hospital Blood Bank and laboratory staff, were used as reference for the laboratory parameters analyzed. Four of them were found with asymptomatic anemia (Hbg values, 9.2–11.5 g/dL) associated with iron deficiency.

A group of 17 asymptomatic carriers of the gene mutation TTR V30M (5 males, 12 females, aged 21 to 69 years) was characterized for all parameters studied. One of them was excluded due to the presence of microcytic anemia associated with iron, vitamin B12, and folic acid deficiencies.

In addition, Epo levels were evaluated in a group of 14 patients with mild to moderate chronic renal insufficiency randomly selected from the nephrology outpatient clinic. Patients with diabetes or renal cysts were excluded. The clearance of creatinine was, on average, 33.9 ± 15.1 (9.4–62.7) mL/min.

All controls were enrolled after informed consent, and approval of the local ethical committee was obtained.

Clinical and laboratory parameters

The demographic and clinical data analyzed were: age, sex, the evolution time of neuropathy, and presence and duration of infection. All patients were evaluated by the same medical team, and categorized according to a modified disability scoring system for neurologic symptoms: score I, sensory disturbances in the extremities, but preserved walking capacity; score II, difficulties in walking, but without the need for a walking stick; score IIIA, one walking stick or one crutch required for walking; score IIIB, two walking sticks or crutches required; and score IV, patients in a wheelchair, or bed confined. Presenting symptoms were sensitive neuropathy in 75.5% of patients, weight loss in 40%, diarrhea and/or constipation in 25.7%, and vomiting in 10%. Sexual dysfunction was a presentation symptom in 45.8% of men. At the evaluation time, the neurologic involvement was classified as stage 0 to II in 69% of patients, stage III in 19.5%, and stage IV in 11.5%.

Laboratory data collected for each group included the hematologic parameters hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocyte counts; the serum levels of iron, transferrin, ferritin, transferrin saturation, vitamin B12, folates, creatinine, urea, and erythropoietin; and proteinuria. Reference values for serum Epo levels were first established in the healthy control population without anemia ($N = 40$). The average serum Epo level was 10.3 ± 2.3 (4.1–23) mU/mL, in accordance with published data [5]. A significant correlation was found between Epo and hemoglobin values ($r = 0.458$; $P = 0.003$). In order to define erythropoietin levels as appropriate or inappropriate for a given hemoglobin level, the observed values were systematically compared with the expected values, estimated according to the logarithmic regression equation of Epo against hemoglobin in control subjects. The regression equation was: Epo = 75.19–24.77 × Ln (Hbg). In addition, to define the expected Epo values in the presence of anemia, a new logarithmic regression equation of Epo against hemoglobin was obtained in the control population including anemic subjects ($N = 46$). The regression equation was: Epo = 208.66–75.377 × Ln (Hbg) ($r = 0.742$; $P = 0.0001$).

Definitions

For the purpose of statistical analysis, FAP patients were divided in 4 groups: 1, FAP with anemia and normal renal function; 2, FAP with anemia and chronic renal insufficiency; 3, FAP without anemia and normal renal function; 4, FAP without anemia and chronic renal insufficiency (CRI).

Anemia

Anemia was considered for hemoglobin levels lower than 11.5 mg/dL in men, and lower than 11.0 mg/dL in women. These cut-off values are routinely used in our current protocols as markers to decide to treat anemia, in accordance with European guidelines to the treatment of anemia of chronic renal failure [6].

Chronic renal insufficiency and estimation of kidney function

Patients with glomerular filtration rate (GFR) of 60 to 41 mL/min, 40 to 21 mL/min, and 20 mL/min or below are classified as having mild, moderate, and advanced degrees of chronic renal insufficiency, respectively [7]. Due to the inability of many patients to accurately collect timed urine samples, the creatinine clearance was estimated by the Cockcroft-Gault equation, corrected for women and low muscular mass. Kidney function estimated by creatinine/creatinine clearance in patients with nephrotic syndrome could be overestimated compared with the function obtained by Cr-EDTA clearance. In a subgroup of 15 patients (11 males, 4 females) with a mean serum creatinine of 0.94 ± 0.21 (0.6–1.3), the estimation of the renal function was done in parallel by the Cockcroft-Gault equation and by the radionuclide markers: ^{99m}Tc-DTPA ($N = 12$) and ^{99m}Tc-MAG3. We verified that GFR evaluated by radionuclide markers was, on average, 5 mL/min

lower than that estimated by the Cockcroft-Gault equation (data not shown). Based on these results, we defined renal insufficiency when creatinine clearance by radionuclide markers was lower than 60 mL/min, corresponding to a creatinine clearance by Cockcroft-Gault equation lower than 65 mL/min.

Autonomic dysfunction

Autonomic dysfunction was considered when one or more of the following symptoms were present: orthostatic hypotension, gastrointestinal motility disturbances, bladder dysfunction, or rhythm disturbances motivating a definitive pacemaker implantation.

Statistical analysis

Results were expressed as mean ± standard deviation or median (interquartile range), unless otherwise stated.

Continuous variables distribution was assessed by Kolmogorov-Smirnov test.

Linear regression analysis was used to estimate the coefficients of the linear equation that best predict the value of the dependent variable (erythropoietin) from hemoglobin as an independent variable.

Differences between values of related data (observed and expected Epo) were analyzed by Student *t* test for paired samples or Wilcoxon signed-rank test. Continuous variables were compared between groups by Student *t* test for independent samples. The correlation analysis between quantitative variables was performed using Pearson's correlation test.

All data were analysed with SPSS software for Windows (version 11.5, Chicago, IL, USA), and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Prevalence of anemia in FAP patients

Anemia was present in 41 of 165 symptomatic FAP patients (24.8%), similar in both genders (Table 1). In all cases, the anemia was normochromic and normocytic, and no abnormalities in serum folic acid or serum vitamin B12 were found. Although low transferrin saturation values (≤10%) were found in 14 anemic patients (2 males and 3 females with NRF; 2 males and 7 females with CRI), only 2 patients had laboratory criteria of concomitant iron deficiency (i.e., abnormally low values of both transferrin saturation and serum ferritin). In the remaining patients, serum ferritin values were normal to high. The distribution of patients according to the defined clinical groups (see **Methods**) and the laboratory parameters analyzed for characterization of anemia are summarized in Table 2.

The clinical characterization of anemic patients in comparison with the nonanemic patients is summarized in Table 1. The anemic patients had, on average, an evolution time of symptomatic disease significantly higher ($P = 0.003$) than nonanemic patients (9.0 and 5.0 years, respectively), with a more severe neurologic involvement. Chronic renal insufficiency was present in 75.6% of the anemic patients (creatinine clearance ranging from 22.6–64.5 mL/min), and was classified as mild (equal or higher to 41 mL/min) in 19 of the 31 anemic patients with chronic renal insufficiency (61.3%). In the group of the nonanemic patients, renal insufficiency was present in 24.2% of them. Concomitant infection was observed at the time of evaluation in 18 patients. The most common infections were acute urinary tract infections (in 8 patients) and infected wounds (in 8 patients, 6 chronically infected). Pneumonia was present in 1 case, and cholecystitis in another case. The presence of infections was more common in anemic than in nonanemic patients, although the prevalence of chronic infection (duration >1 month) was similar in both groups. No significant differences were observed on leukocyte or lymphocyte counts between the 2 groups. No correlation was found between the presence of infection and serum Epo levels (data not shown).

Table 1. Demographic and clinical data of the anemic and nonanemic patients

	Anemia	No anemia	
Number of patients	41	124	
Male/Female	22/19	68/56	
Age *years*	43 ± 9	41 ± 11.8	NS
Disease evolution time	9 ± 5	5 ± 4	$P = 0.003$
Neurologic stage			
Stage I—II	19 (46.4%)	93 (75%)	
Stage III	13 (31.7%)	18 (14.5%)	
Stage IV	9 (21.9%)	13 (10.5%)	
Renal failure	31 (75.6%)	30 (24.2%)	
Creat Cl ≥41 mL/min	19/31 (61.3%)	7/30 (23.3%)	
Proteinuria >1 g/day	15/41 (36.6%)	15/124 (12.1%)	
History of infection	19 (46.4%)	21 (16.9%)	
Duration >1 month	6/19	8/21	
Leukocytes/mm^3	8.03 ± 3.6	7.17 ± 1.9	NS
Lymphocytes/mm^3	1.5 ± 0.4	1.97 ± 1.5	NS

Anemic patients had a more severe neurologic involvement, and a higher prevalence of infection.

Erythropoietin levels in FAP patients

Serum erythropoietin levels were evaluated in a total of 124 symptomatic FAP patients (75.2%). In order to classify the individual Epo serum levels as appropriate or not for the degree of anemia, the ratio of observed to expected Epo (O/E) values was determined in all patients and compared among groups. The results are summarized in Table 3. In general, FAP patients presented with significantly lower serum erythropoietin levels than healthy control patients ($P = 0.003$). In 21 patients (17.5%), the O/E Epo ratio was lower than 0.25, with undetectable levels in 9 of them. In all FAP groups, the observed Epo levels were, on average, lower than expected for the hemoglobin

Table 2. Comparative analysis of laboratorial data from FAP patients and control groups: healthy, diabetics, chronic renal insufficiency (CRI), and asymptomatic gene carriers (AC)

	Anemia FAP patients		No anemia FAP patients		Control groups		
	NRF ($N = 7$)	CRI ($N = 28$)	NRF ($N = 61$)	CRI ($N = 28$)	AC ($N = 16$)	CRI ($N = 14$)	Healthy ($N = 40$)
Hbg *g/dL*	9.2 ± 1.9[a]	9.6 ± 1.1	13.9 ± 1.4	12.6 ± 1.0	13.6 ± 1.2	12.2 ± 1.7	13.8 ± 1.3
MCV *fl*	86.7 ± 13.9	91.9 ± 5.1	91.4 ± 3.8	93.9 ± 3.4	90.5 ± 4.8	91.5 ± 9.0	89.0 ± 5.0
MCHC *g/dL*	32.7 ± 2.1	32.9 ± 1.3	34.0 ± 0.8	33.4 ± 1.1	34.2 ± 0.6	33.6 ± 1.0	34.0 ± 1.0
Transferrin saturation %	15.3 ± 12.0	19.2 ± 14.3	30.9 ± 13.5	33.2 ± 18.1	31.7 ± 10.4	24.2 ± 7.3	28.0 ± 10.0
Ferritin *ng/mL*	204.6 ± 172.8	161.1 ± 147.4	96.1 ± 77.1	137.3 ± 160.5	59.1 ± 50.6	158.7 ± 105.5	63.2 ± 152.5

NFR, normal renal function; CRI, chronic renal insufficiency. All parameters were in normal range except serum erythropoietin, present in low levels independently of the presence or absence of anemia or renal failure.
[a]Results presented as mean ± standard deviation.

Table 3. Observed (O) and expected (E) erythropoietin levels in all study groups

	Anemia FAP patients		No anemia FAP patients		Control groups		
	NRF ($N = 7$)	CRI ($N = 28$)	NRF ($N = 61$)	CRI ($N = 28$)	AC ($N = 16$)	CRI ($N = 14$)	Healthy ($N = 40$)
Creatinine clearance (mL/min)	77.6 ± 10.2[a]	43.0 ± 11.7	104.1 ± 21.1	55.1 ± 17.3	111.8 ± 30.4	33.9 ± 15.1	105.2 ± 19.7
Observed EPO (mU/mL)	46.2 ± 57.4[c]	13.8 ± 13.0[e]	7.9 ± 4.4[d]	9.3 ± 5.9	9.2 ± 3.7	14.7 ± 7.9	10.3 ± 5.0
Expected EPO (mU/mL)	43.3 ± 17.1	38.8 ± 9.3	10.1 ± 2.5	12.1 ± 2.6	11.9 ± 4.7	13.5 ± 3.2	10.3 ± 2.3
Epo O/E <0,8	4 (57%)[b]	27 (96%)	31 (51%)	19 (68%)	7 (44%)	5 (36%)	13 (28%)
Epo O/E 0.8–1.2	1 (14%)	0	20 (33%)	6 (21%)	8 (50%)	2 (14%)	21 (46%)
Epo O/E >1.2	2 (29%)	1 (4%)	10 (16%)	3 (11%)	1 (6%)	7 (50%)	12 (26%)

The number of patients and respective percentage with a ratio O/E Epo <0.8, 0.8–1.2, and >1.2 are presented.
[a]Results presented as mean ± standard deviation.
[b]Number of patients and percentage.
[c]The anemic FAP and normal renal function patients group includes 1 patient with 2 years of clinical disease, an iron deficiency anemia, and serum Epo level of 163 mU/mL. After excluding this patient, the average serum Epo level in this group was 26.7 ± 27.7 mU/mL for an expected level of 39.4 ± 15.1 mU/mL.
[d]$P < 0.005$.
[e]$P < 0.0001$

level, except in the group of anemic FAP with normal renal function (see Table 3). Differences between observed and expected Epo levels were most highly significant in the groups of FAP patients with renal insufficiency either presenting with anemia ($P < 0.0001$) or not ($P = 0.0005$). Surprisingly, a highly significant difference was also observed in the group of FAP patients who had neither CRI nor anemia ($P = 0.003$), and also in the group of asymptomatic carriers of the gene mutation TTR V30M ($P = 0{,}03$). In all control groups, including the group with non-FAP CRI, no differences between observed and expected Epo levels were seen (see Table 3). In order to evaluate the influence of proteinuria on Epo serum levels, FAP patients were divided into 2 subgroups, with proteinuria >1 g/day ($N = 27$), and proteinuria <1 g/day ($N = 97$). The average Epo level was not different between the subgroups with or without proteinuria >1 g/day (12.9 ± 15.4 mU/mL and 11.4 ± 17.6 mU/mL, respectively).

The relative frequencies of subjects with observed Epo levels lower (O/E <0.8), similar (O/E = 0.8–1.2), or higher (O/E >1.2) than expected was evaluated in all study groups (see Table 3). A clear shift to low O/E values is observed in FAP patients. The shift is already evident in asymptomatic carriers of the gene mutation TTR V30M (O/E <0.8 in 44%), is increasingly higher with clinical disease without CRI (O/E <0.8 from 51%–57%), and is maximal in the presence of CRI and anemia (O/E <0.8 in 96%).

Erythropoietin levels in asymptomatic carriers of the gene mutation TTR V30M

The 16 asymptomatic carriers of the gene mutation TTR V30M presented with serum haemoglobin levels, on average, 13.6 ± 1.2 g/dL. As described before, observed serum erythropoietin levels were lower than the expected in 44% of subjects ($N = 7$). The time of follow-up after the laboratory evaluation was, on average, 20.2 ± 10.7 (7–42) months. During this period, 6 AC became symptomatic, on average, after 18.1 ± 10.9 (2–22) months. The other 10 individuals remained free of symptoms after 21.4 ± 11 months of follow-up. These include 6 of the 7 patients who presented with O/E Epo <0.8.

Erythropoietin levels and autonomic dysfunction

FAP patients were divided in 2 subgroups according to the presence ($N = 32$) or absence ($N = 29$) of clinical autonomic dysfunction. Patients with dysautonomy had an

average Epo value of 8.2 ± 4.8 mU/mL, not significantly different from the average value presented by those without dysautonomy (7.8 ± 4.0 mU/mL; $P = 0.719$). In spite of a more severe autonomic dysfunction in anemic FAP patients (orthostatic hypotension, 58%, pacemaker, 19.4%) than in nonanemic patients (orthostatic hypotension, 22%, pacemaker, 7.5%), no significant differences on Epo levels were found between patients with or without autonomic disturbances.

Erythropoietin levels and chronic renal insufficiency (CRI)

In order to evaluate the impact of CRI on Epo levels outside the setting of FAP, a control group of non-FAP patients with CRI was analyzed for serum Epo. The average clearance of creatinine in this group was 33.9 ± 15.1 mL/min, and the mean hemoglobin level was 12.2 ± 1.7 g/dL (see Table 3). No significant differences were seen between the observed and expected Epo levels. The observed Epo level was 14.7 ± 7.9 mU/mL for an average expected Epo level of 13.5 ± 3.2 mU/mL. In spite of a more severe renal insufficiency in this group compared with the nonanemic FAP patients analyzed (creatinine clearances of 33.9 ± 15.1 mL/min and 55.1 ± 17.3 mL/min, respectively), the average observed Epo level was higher in the first group.

DISCUSSION

Anemia in FAP is a common feature, occurring in 24.8% of the Portuguese patients analyzed in the present study. Its appearance was late, on average after 9 years of symptomatic disease, and affected males and females equally. The anemia was normocytic and normochromic. B12 vitamin and folate serum levels were normal, and iron stores were also normal in most of the patients. Therefore, a deficiency of those nutrients could not be implicated in the genesis of the anemia. Inappropriately low Epo levels were commonly observed in FAP patients, even at early clinical stages of disease, independent of the presence of chronic renal insufficiency, pointing to a putative role of Epo deficiency in the genesis of anemia in FAP.

Several clinical conditions are known to be associated with low serum Epo levels. In chronic renal insufficiency, a decreased Epo production leads to anemia, usually with creatinine clearance lower than 40 mL/min/1.73 m^2 [8]. Therefore, the presence of CRI in FAP patients is a relevant parameter to explain, at least in part, the finding of inappropriately low Epo values in anemic patients. It does not explain, however, the consistent finding of inappropriately low Epo levels in other groups of patients without CRI, or in asymptomatic carriers of the gene mutation TTR V30M, preceding clinical disease. Moreover, Epo levels were lower in FAP patients than in control non-FAP patients with a greater degree of CRI.

Anemia with low serum Epo levels has also been reported in chronic inflammatory diseases [9–12]. Inflammatory cytokines inhibit the production of erythropoietin as well as the growth of erythroid progenitor cells, impairing the response to recombinant erythropoietin [13–15]. Consequently, in these situations, the response to treatment with recombinant erythropoietin (rhEpo) is usually "blunted." A preliminary study performed in 38 of the patients reported here had shown a great improvement of anemia when treated with low doses of rhEpo [3], therefore not supporting the hypothesis of an inhibitor role of cytokines in the defective production of Epo and blood marrow response.

The presence of nephrotic syndrome may contribute to reduce the Epo production [16–20]. This possibility was excluded in the present group of FAP patients by the finding of similar values in patients with or without proteinuria.

Although autonomic neuropathy is involved in the genesis of anemia [21], in the present study, the Epo levels were not significantly different between FAP patients with or without clinical autonomic disturbances, suggesting that other factors are involved in the decrease of erythropoietin production.

Taken together, the results presented here suggest that an important defective production of Epo may occur in TTR V30M FAP, a defect that may be worsened by the presence of mild renal insufficiency. The mechanism how Epo production could be impaired in this condition is still not known.

Hypoxia is generally considered the major stimulus for the erythropoietin production, with rapid increase in renal production of Epo through an exponential increase in the number of Epo-producing cells [22]. The precise nature of the mammalian oxygen sensor remains unclear, several lines of evidence indicating that is a heme protein [23]. In the adult, the kidney is the major site of erythropoietin production. The Epo-producing cells were identified as fibroblast-like type I interstitial cells, localized in the peritubular interstitium [24–26]. The inability to create a cellular line of Epo-producing cells from kidney suggests that the expression of these cells depends on interstitial environment. In a previous study we have shown that interstitial amyloid deposits in renal biopsy were always present in the medullary zone, even in the absence of clinical nephropathy. In the presence of proteinuria and/or renal insufficiency, the renal cortex was also involved with additional glomerular and vascular deposits [27]. The low levels of Epo in FAP patients, even in carriers of the TTR V30M mutation, the inability to respond to anemia with an increase in erythropoietin production in absence of renal failure, and the development of anemia with mild renal insufficiency (mean creatinine

clearance of 43 mL/min) suggest a decrease of interstitial producing-Epo cells or unfavorable interstitial conditions that block the Epo-producing cells expression. These abnormalities could be related to the presence of amyloid deposits in the renal interstitium. The low Epo levels observed in asymptomatic carriers could be explained either by the presence of early renal amyloid deposits, or the influence of factors other than amyloid itself in the Epo-producing cells expression, and consequently, the Epo production.

CONCLUSION

The use of recombinant human erythropoietin proved to be efficient in the treatment of these patients [3], which suggests a normal functional bone marrow. It seems clear that anemia in FAP type I is caused by a defective endogenous Epo production and should constitute an indication for recombinant human erythropoietin use outside the setting of uremia.

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